

Claims

1           1. A method of directing a cellular immune response  
2 in a mammal, said method comprising administering to said  
3 mammal an effective amount of therapeutic cells, said  
4 therapeutic cells expressing a membrane-bound, proteinaceous  
5 chimeric receptor comprising (a) an extracellular portion  
6 which is capable of specifically recognizing and binding  
7 said target cell or said target infective agent, and (b) an  
8 intracellular portion which is capable of signalling said  
9 therapeutic cell to destroy a receptor-bound target cell or  
10 a receptor-bound target infective agent.

1           2. The method of claim 1, wherein said target cell  
2 is a host cell infected with an infective agent, a tumor or  
3 cancerous cell, or an autoimmune-generated cell.

1           3. The method of claim 1, wherein said cellular  
2 response is MHC-independent.

1           4. The method of claim 1, wherein said  
2 intracellular portion is the signal-transducing portion of a  
3 T cell receptor protein, a B cell receptor protein, or an Fc  
4 receptor protein, or a functional derivative thereof.

1           5. The method of claim 1, wherein said chimeric  
2 receptor further comprises a transmembrane portion of said T  
3 cell receptor protein, said B cell receptor protein, or said  
4 Fc receptor protein.

1           6. A method of directing a cellular immune response  
2 in a mammal, said method comprising administering to said  
3 mammal an effective amount of therapeutic cells, said  
4 therapeutic cells expressing a membrane-bound, proteinaceous  
5 chimeric receptor, said receptor comprising (a) an

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6 extracellular portion which is capable of specifically  
7 recognizing and binding said target cell or said target  
8 infective agent, and (b) a transmembrane portion which is  
9 capable of signalling said therapeutic cell to destroy a  
10 receptor-bound target cell or a receptor-bound target  
11 infective agent.

1 7. The method of claim 6, wherein, following  
2 binding of said extracellular portion to said agent or said  
3 cell, said transmembrane portion oligomerizes with a  
4 cytolytic signal-transducing protein of said therapeutic  
5 cell resulting in destruction of said receptor-bound cell or  
6 agent.

1 8. The method of claim 6, wherein said  
2 transmembrane portion comprises an oligomerizing portion of  
3 a T cell receptor protein, a B cell receptor protein, or an  
4 Fc receptor protein, or a functional derivative thereof.

1 9. The method of claim 4, wherein said T cell  
2 receptor protein is  $\zeta$ .

1 10. The method of claim 9, wherein said chimeric  
2 receptor comprises amino acids 421-532 of SEQ ID NO: 6, or a  
3 functional cytolytic signal-transducing derivative thereof.

1 11. The method of claim 9, wherein said chimeric  
2 receptor comprises amino acids (a) 423-455; (b) 438-455; (c)  
3 461-494; or (d) 494-528 of SEQ ID NO: 6.

1 12. The method of claim 8, wherein said T cell  
2 receptor protein is  $\zeta$ .

1 13. The method of claim 12, wherein said chimeric  
2 receptor comprises amino acids 400-420 of SEQ ID NO: 6.

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1 14. The method of claim 4, wherein said T cell  
2 receptor protein is  $\eta$ .

1 15. The method of claim 14, wherein said chimeric  
2 receptor comprises amino acids 421-575 of SEQ ID NO: 4, or a  
3 functional cytolytic signal-transducing derivative thereof.

1 16. The method of claim 14, wherein said chimeric  
2 receptor comprises amino acids (a) 423-455; (b) 438-455; (c)  
3 461-494; or (d) 494-528 of SEQ ID NO: 4.

1 17. The method of claim 8, wherein said T cell  
2 receptor protein is  $\eta$ .

1 18. The method of claim 17, wherein said chimeric  
2 receptor comprises amino acids 400-420 of SEQ ID NO: 4.

1 19. The method of claim 4, wherein said Fc receptor  
2 protein is  $\gamma$ .

1 20. The method of claim 19, wherein said chimeric  
2 receptor comprises amino acids 421-462 of SEQ ID NO:5, or a  
3 functional cytolytic signal-transducing derivative thereof.

1 21. The method of claim 8, wherein said Fc receptor  
2 protein is  $\gamma$ .

1 22. The method of claim 21, wherein said chimeric  
2 receptor comprises amino acids 402-419 of SEQ ID NO:5.

1 23. The method of claim 21, wherein said chimeric  
2 receptor comprises amino acids Tyr282-Tyr298 inclusive of  
3 Fig. 15A.

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1           24. The method of claims 4 or 8, wherein said Fc  
2 receptor protein is human FcγRIII, human FcRIIγA, or human  
3 FcRIIγC.

1           25. The method of claims 4 or 8, wherein said T  
2 cell receptor protein is CD3 delta.

1           26. The method of claim 25, wherein said chimeric  
2 receptor protein comprises amino acids 132-171 of Fig. 16  
3 (SEQ ID NO: 24).

1           27. The method of claims 4 or 8, wherein said T  
2 cell receptor protein is T3 gamma.

1           28. The method of claim 27, wherein said chimeric  
2 receptor protein comprises amino acids 140-182 of Fig. 17  
3 (SEQ ID NO: 25).

1           29. The method of claims 4 or 8, wherein said B  
2 cell receptor protein is mb1.

1           30. The method of claim 29, wherein said chimeric  
2 receptor protein comprises amino acids 162-220 of Fig. 18  
3 (SEQ ID NO: 26).

1           31. The method of claims 4 or 8, wherein said B  
2 cell receptor protein is B29.

1           32. The method of claim 31, wherein said chimeric  
2 receptor protein comprises amino acids 183-228 of Fig. 19  
3 (SEQ ID NO: 27).

1           33. The method of claims 1 or 6, wherein said  
2 therapeutic cells are selected from the group consisting of:  
3           (a) T lymphocytes;

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- 4 (b) cytotoxic T lymphocytes:  
5 (c) natural killer cells;  
6 (d) neutrophils;  
7 (e) granulocytes;  
8 (f) macrophages;  
9 (g) mast cells;  
10 (h) HeLa cells; and  
11 (i) embryonic stem cells (ES).

1 34. The method of claims 1 or 6, wherein said  
2 target infective agent is an immunodeficiency virus.

1 35. The method of claims 1 or 6, wherein said  
2 extracellular portion comprises an HIV envelope-binding  
3 portion of CD4, or a functional HIV envelope-binding  
4 derivative thereof.

1 36. The method of claims 1 or 6, wherein said HIV-  
2 envelope binding portion of CD4 comprises the peptide  
3 encoded by nucleotides 1-369 of SEQ ID NO:1.

1 37. The method of claims 1 or 6, wherein said  
2 therapeutic cells further express a membrane-bound,  
3 proteinaceous chimeric receptor comprising (a) an  
4 extracellular portion which is capable of specifically  
5 recognizing and binding said target cell or said target  
6 infective agent, and (b) an intracellular portion which is  
7 derived from CD28.

1 ~~38. The method of claims 1 or 6, wherein said~~  
2 ~~therapeutic cells destroy said receptor-bound target cell or~~  
3 ~~target infective agent by cytolysis.~~

1 39. A cell which expresses a proteinaceous  
2 membrane-bound chimeric receptor, said receptor comprising

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3 (a) an extracellular portion which is capable of  
4 specifically recognizing and binding a target cell or a  
5 target infective agent, and (b) an intracellular portion  
6 derived from a T cell receptor, a B cell receptor, or an Fc  
7 receptor which is capable of signalling said cell to destroy  
8 a receptor-bound target cell or receptor-bound target  
9 infective agent.

1           40. The cell of claim 39, wherein said target cell  
2 is a host cell infected with an infective agent, a tumor or  
3 cancerous cell, or an autoimmune-generated cell.

1            41. The cell of claim 39, wherein said binding is  
2 MHC-independent.

1           42. The cell of claim 39, wherein said  
2 intracellular portion is the signal-transducing portion of a  
3 T cell receptor protein, a B cell receptor protein, or an Fc  
4 receptor protein, or a functional derivative thereof.

1           43. The cell of claim 42, wherein said chimeric  
2 receptor further comprises a transmembrane portion of said T  
3 cell receptor protein, said B cell receptor protein, or said  
4 Fc receptor protein.

44. A cell expressing a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or a receptor-bound target infective agent.

1           46. The cell of claim 44, wherein said binding is  
2 MHC-independent.

1           48. The cell of claim 42, wherein said T cell  
2    receptor protein is  $\zeta$ .

1           50. The cell of claim 48, wherein said chimeric  
2 receptor comprises amino acids (a) 423-455; (b) 438-455; (c)  
3 461-494; or (d) 494-528 of SEQ ID NO. 6.

~~1 52. The cell of claim 51, wherein said chimeric~~  
2 receptor comprises amino acids 400-420 of SEQ ID NO: 6.

1            53. The cell of claim 42, wherein said T cell  
2    receptor protein is ~~an~~

1           54. The cell of claim 53, wherein said chimeric  
2 receptor comprises amino acids 421-575 of SEQ ID NO: 4, or a  
3 functional cytolytic signal-transducing derivative thereof.

1           55. The cell of claim 53, wherein said chimeric  
2 receptor comprises amino acids (a) 423-455; (b) 438-455; (c)  
3 461-494; or (d) 494-528 of SEQ ID NO: 4.

1           56. The cell of claim 47, wherein said T cell  
2 receptor protein is  $\eta$ .

1           57. The cell of claim 56, wherein said chimeric  
2 receptor comprises amino acids 400-420 of SEQ ID NO: 4.

1           58. The cell of claim 42, wherein said Fc receptor  
2 protein is  $\gamma$ .

1           59. The cell of claim 58, wherein said chimeric  
2 receptor comprises amino acids 421-462 of SEQ ID NO:5, or a  
3 functional cytolytic signal-transducing derivative thereof.

1           60. The cell of claim 47, wherein said Fc receptor  
2 protein is  $\gamma$ .

1           61. The cell of claim 60, wherein said chimeric  
2 receptor comprises amino acids 402-419 of SEQ ID NO: 5.

1           62. The cell of claim 60, wherein said chimeric  
2 receptor comprises amino acids Tyr282-Tyr298 inclusive of  
3 Fig. 15A.

1           63. The cell of claims 42 or 47, wherein said Fc  
2 receptor protein is human Fc $\gamma$ RIII, human FcRII $\gamma$ A, or human  
3 FcRII $\gamma$ C.

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1 64. The cell of claims 42 or 47, wherein said T  
cell receptor protein is CD3 delta.

1 65. The cell of claim 64, wherein said chimeric  
2 receptor protein comprises amino acids 132-171 of Fig. 16  
3 (SEQ ID NO: 24).

1 66. The cell of claims 42 or 47, wherein said T  
2 cell receptor protein is T3 gamma.

1 67. The cell of claim 66, wherein said chimeric  
2 receptor protein comprises amino acids 140-182 of Fig. 17  
3 (SEQ ID NO: 25).

1 68. The cell of claims 42 or 47, wherein said B  
2 cell receptor protein is mb1.

1 69. The cell of claim 68, wherein said chimeric  
2 receptor protein comprises amino acids 162-220 of Fig. 18  
3 (SEQ ID NO: 26).

1 70. The cell of claims 42 or 47, wherein said B  
2 cell receptor protein is B29.

1 71. The cell of claim 70, wherein said chimeric  
2 receptor protein comprises amino acids 183-228 of Fig. 19  
3 (SEQ ID NO: 27).

1 72. The cell of claims 39 or 44, wherein said  
2 extracellular portion comprises the ligand-binding portion  
3 of a receptor, the receptor-binding portion of a ligand, the  
4 antigen-binding portion of an antibody, or a functional  
5 derivative thereof.

1 73. The cell of claims 39 or 44, wherein said target  
2 infective agent is an immunodeficiency virus or said target  
3 cell is a host cell infected with an immunodeficiency virus.

1 74. The cell of claim 73, wherein said  
2 extracellular portion comprises an HIV envelope-binding  
3 portion of CD4, or a functional derivative thereof.

1 75. The cell of claim 73, wherein said HIV-envelope  
2 binding portion of CD4 comprises the peptide encoded by  
3 nucleotides 1-369 of SEQ ID NO:1.

1 76. The cell of claims 39 or 44, wherein said cell  
2 further expresses a membrane-bound, proteinaceous chimeric  
3 receptor comprising (a) an extracellular portion which is  
4 capable of specifically recognizing and binding said target  
5 cell or said target infective agent, and (b) an  
6 intracellular portion which is derived from CD28.

1 77. The cell of claims 39 or 44, wherein said cell  
2 destroys said receptor-bound target cell or target infective  
3 agent by cytolysis.

1 78. A cell which expresses a proteinaceous  
2 membrane-bound chimeric receptor, said receptor comprising  
3 (a) an extracellular portion which is capable of  
4 specifically recognizing and binding a target cell or a  
5 target infective agent, and (b) an intracellular portion  
6 derived from a T cell receptor CD3, zeta, or eta  
7 polypeptide, a B cell receptor, or an Fc receptor.

1 79. A cell which expresses a proteinaceous  
2 membrane-bound chimeric receptor, said receptor comprising  
3 (a) an extracellular portion which is capable of  
4 specifically recognizing and binding a target cell or a

5 target infective agent, and (b) a transmembrane portion  
6 derived from a T cell receptor CD3, zeta, or eta  
7 polypeptide, a B cell receptor, or an Fc receptor.

1 80. The cell of claims 78 or 79, wherein said  
2 chimeric receptor includes a CD16 or CD5 extracellular  
3 portion.

1 81. The cell of claims 78 or 79, wherein said  
2 chimeric receptor includes a CD5 or CD7 transmembrane  
3 portion.

1 82. The cell of claims 78 or 79, wherein said  
2 chimeric receptor includes a CD5 or CD7 intracellular  
3 portion.

1 83. DNA encoding a proteinaceous membrane-bound  
2 chimeric receptor, said receptor comprising (a) an  
3 extracellular portion which is capable of specifically  
4 recognizing and binding a target cell or a target infective  
5 agent, and (b) an intracellular portion derived from a T  
6 cell receptor, a B cell receptor, or an Fc receptor which is  
7 capable of signalling said cell to destroy a receptor-bound  
8 target cell or receptor-bound target infective agent.

1 84. DNA encoding a proteinaceous membrane-bound  
2 chimeric receptor, said receptor comprising (a) an  
3 extracellular portion which is capable of specifically  
4 recognizing and binding a target cell or a target infective  
5 agent, and (b) a transmembrane portion derived from a T cell  
6 receptor, a B cell receptor, or an Fc receptor which is  
7 capable of signalling said cell to destroy a receptor-bound  
8 target cell or a receptor-bound target infective agent.

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